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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,816	LEMMENS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-22,28-33 and 37-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-22,28-33 and 37-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of the Request for Continued Examination and Amendments filed on December 4, 2003 and the Information Disclosure filed on January 12, 2004 is acknowledged. Claims **1-2, 4-22, 28-33, and 37-47** are pending in this application. Claims 3 and 23-27 stand cancelled. Claims 34-36 have not been entered.

Information Disclosure Statement

The information disclosure statement filed January 12, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. In instant case, the Information Disclosure fails to supply a copy of the non-patent literature cited on page 4 of the Disclosure and thus has not been considered. The WIPO document cited on page 3 of the Disclosure has been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 4-7, 9, 11, 14, 15-18, 22, 37-41, and 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303).

Davison et al teach the pharmaceutically acceptable salts of amlodipine such as instant amlodipine maleate, in a pharmaceutical composition for treating angina and hypertension. Davison compares the amlodipine salts to four criteria: (1) Good bioavailability of the drug is dependent on good solubility. Thus, the preferred pH of the composition is taught to be close to that of the blood pH of 7.4 since it is readily biocompatible. Table 1 states that the pH of instant amlodipine maleate is 4.8. (2) Good stability is required. Thus, the salts are formulated into tablets by blending microcrystalline cellulose and dibasic calcium phosphate, followed by compression. Capsules are formulated by blending mannitol and starch. Instant sodium starch glycollate is taught on Table 3. The sealed vials are stored at 50 degrees Celsius and 75 degrees Celsius for up to three weeks to check for chemical breakdown. The Table on column 3 states the relative stability of each salt. (3) Non-hydroscopicity provides for s stable formulation. Davison teaches that moisture can act as a vector for hydrolysis and chemical breakdown. Davison states that only maleate, tosylate, and besylate salts do not pick up moisture when exposed to 75% relative humidity at 37 degrees Celsius for 24 hours. Further, when the stated salts are exposed to 95% humidity at 30 degrees

Celsius for three days both besylate and maleate remain anhydrous. (4) Good processability. See column 2, line 21 to column 3, line 35.

Davison et al do not specify the instant pH of the composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was to look at the guidance provided by Davison et al and manipulate the pH of the composition. It is deemed prima facie obvious to optimize conditions set forth in the prior art since it is not considered inventive to discover the optimum or workable ranges. This guidance of adjusting the pH is further provided by Davison since Davison teaches sodium glycollate and dibasic calcium phosphate, which are routinely utilized in the art to adjust pH to, desired level. Thus, Davison discloses the pH of the instant maleate is 4.8 and the use of dibasic calcium phosphate in the composition; therefore a skilled artisan would recognize that this combination would yield a pH within the recited range. Therefore, one would be motivated to adjust the pH to discover the optimum pH range of the composition since the prior art clearly set forth the need to do so.

Furthermore, it is deemed obvious to a skilled artisan to determine suitable excipients ranges through routine experimentation to obtain optimal results since these are manipulative parameters.

Response to Amendment

The Declaration under 37 CFR 1.132 filed September 5, 2003 is insufficient to overcome the rejection over Davison et al as set forth in the last Office action because: Firstly, the examiner points out that the claims are directed to generic solid compositions and the Rule 132 Declaration specifically utilizes tablet formulations.

Therefore, the claims are not commensurate in scope. Secondly, the examiner points out that the claims broadly recite amlodipine maleate and excipients. However, the Rule 132 declaration utilizes a *specific* formulation with *specific* excipients. The claims do not reflect this specific formulation with specific concentrations and thus again are not commensurate in scope. It should be further noted that a single specific formulation does not establish a generic concept. Thirdly, the examiner points out that Davison's experiments for "good stability of the solid state" were done under the following conditions: 50 degrees and 75 degrees Celsius for three weeks. Applicant's tests were conducted at 60 degrees and 40 degrees Celsius for four weeks. The applicant then came to the conclusion that Davison's maleate salt was not stable compared to the instant invention's maleate. The examiner points out that in substantiating unexpected results, the conditions must be the same so that the examiner can make a valid judgment based on the data and not external parameters that may affect the eventual outcome of the results. It should be noted that in applicant's numerous arguments of stability, Davison states that when the instant salt is exposed to 95% RH at 30 degrees Celsius for three days, maleate remains anhydrous and does not convert into a dihydrate salt. Clearly the applicant is claiming a difference in degree of stability over time, which again the claims do not reflect.

Response to Arguments

Applicant states that although Davison et al prefer instant maleate salt, the instability problems of the instant salt caused Davison to switch to the besylate salt. Applicant argues that Davison et al fails to solve amlodipine maleate's stability

problems. It is argued that by controlling the pH of the composition, the stability is improved since the formation of impurities is avoided. Thus, the composition can be stored without decomposing. Applicant argues that the specification utilizes a specific grade of calcium phosphate and the pH for calcium phosphate dibasic is listed under the typical properties of 7.3 and 5.1.

Applicant's arguments have been fully considered but they are not persuasive. Firstly, the examiner points out that the prior art clearly recognizes the instability problems of maleate *in solution* and teaches four physiochemical criteria that should be met by amlodipine salts. The examiner points to Davison's teachings on column 2, line 47 wherein he states that "good stability in the solid state is very important for tablets and capsules". Additionally, the art clearly teaches the advantages and disadvantages of each salt. Therefore, it is clear the prior art provides a motivation to find a solution to this instability problem of the desired salt. Not only does the prior art direct a skilled artisan to experiment, the art directs one to the instant maleate by clearly stating this is the preferred salt. See column 1, lines 17. Lastly, the art provides guidance in order to evaluate the instability of the salts and manipulate conditions with the use of conventional excipients.

In regards to applicant's argument that besylate is the preferred salt, the examiner points out that a preferred embodiment does not constitute a teaching away from the broad disclosure of amlodipine salts.

Applicant asserts that one would not be motivated to manipulate the pH of the salt. However, the examiner points out that the manipulation of the pH of a composition

is routinely done in the pharmaceutical art. The examiner points out that the pH of maleate is 4.8 and adding a dibasic phosphate would increase the pH since as recognized by the applicant, the typical properties for phosphate dibasic is a pH of 7.3 and 5.1. Thus, the combination of the dibasic phosphate and instant salt would render Davison's pH within claimed range. Applicant stresses that the type of dibasic phosphate is critical to the composition to yield the desired pH. If the amount and type of buffer used are critical to the invention, the applicant fails to incorporate this into the claims. Even if one were to argue the merits of the dibasic calcium phosphate taught by Davison, the examiner points out that the art also teaches the use of microcrystalline cellulose. This excipient also has a basic pH and places the pH of Davison's composition in applicant's recited range. Lastly, although Davison specifically addresses solubility of injectable formulation, the examiner points out that manipulation of pH for solid compositions is routinely done in the art and one can extend this teaching into solid compositions. One would be motivated to extend the teaching since it provides a starting point in which one can routinely experiment.

Applicant asserts that the instant composition is stable. However, applicant is actually arguing a difference in degree of stability over time. The examiner points out that on column 3, lines 1-30, Davison states that maleate does not pick up moisture, does not intrinsically breakdown, and does not convert into a dihydrate salt even after three days. Therefore, it can be seen that maleate is relatively stable. Lastly, it should be noted that this argument of stability during prolonged storage and the specific time parameter, are not included in the claims. Although the claims are interpreted in light of

the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of EP 0089167.

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate.

Davison et al do not teach the amount of amlodipine maleate.

EP teaches a pharmaceutical composition containing amlodipine and preferable its salt form, amlodipine maleate. Tablets and capsules contain 1 to 10mg preferably to treat cardiac condition (pg. 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant recited range of active. One would be motivated to do so since EP teaches this amount to effectively treat cardiac conditions.

Response to Arguments

Applicant does not argue the merits of the instant rejection; instead applicant discusses the merit of Davison, which has been addressed above.

Claims 10 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of Sherwood et al (5585115).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate.

Davison et al do not teach a coated tablet or specify the type of granulation (wet/dry).

Sherwood et al teach a method of improving compressibility in tablets using microcrystalline cellulose. Sherwood discloses the three general methods of preparing solid dosage forms: dry granulation, direct compression, and wet granulation (col. 1, lines 64-67). Sherwood discloses that the method depends on the drug and excipients. Lastly Sherwood teaches the optional use of a hydrophobic coating to provide a sustained release (col. 12, lines 60-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Davison et al and Sherwood et a. One would be motivated to do so since Sherwood teaches the art of tabletting and practice of utilizing the instant granulation method. One would be motivated to utilize the method of choice depending on the drug and excipients. It should be noted that the choice of method, i.e. moist versus dry, does not change the tablet's material function and thus is deemed an obvious modification of the prior art process.

Furthermore, one would be motivated to look to the guidance provided by Sherwood since Sherwood teaches the use of tablet coatings to provide for sustained release. Therefore, a skilled artisan would be motivated to utilize a coating depending on the drug release pattern desired.

Response to Arguments

Applicant does not argue the merits of the instant rejection; instead applicant discusses the merit of Davison, which has been addressed above.

Claims 21 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison et al (4879303) in view of Sherwood et al (5585115) in further view Schobel (4687662).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate. Sherwood et al teach the method of making a solid dosage form.

The references do not specify the particle size of the active.

Schobel discloses a therapeutic effervescent composition. Schobel teaches the generally the preferred particle size when tabletting a solid dosage form. The reference discloses a particle size less than 100 microns has processing problems such as poor mixing and compressibility. (Col. 4, lines 31-45)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to encompass the teachings of Schobel and utilize particle sizes above 100 microns for a solid dosage form. One would be motivated to do so since Schobel teaches fine particles less than 100 microns tend to cause processing problems such as poor mixing and compressibility. Thus, a skilled artisan would use the instant particle sizes to provide for an efficient tabletting process and one would expect similar results since both Schobel and Davison teach the formulation of solid dosage forms.

Response to Arguments

Applicant does not argue the merits of the rejection rather he discusses the merit of Davison which have been discussed above.

Claims 8, 28-31, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison (4879303) in view of Takatsuka et al (6471946).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate. Davison teaches adjusting the pH of the composition to that of blood or close to blood pH for biocompatibility. Davison teaches the use of excipients for compression aids such microcrystalline cellulose.

Davison does not teach the use of an acid pH-adjusting agent.

Takatsuka teaches an oral composition. The reference teaches conventional pH adjusting agents are citric acid, phosphoric acid, malic acid, and maleic acid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Davison and Takatsuka and utilize acid pH adjusting agents in Davison's composition. One would be motivated to do so with the expectation of similar results since Takatsuka teaches the instant acids are conventional pH-adjusting agents and Davison clearly teaches the use of buffering agents to alter the pH. Furthermore, one would be motivated to do so since Davison incorporates excipients that are basic, which might increase the pH beyond that of the pH of blood; therefore one would use an acidic pH-adjusting agent to lower the pH closer to blood.

Response to Arguments

Applicant does not argue the merits of the instant rejection; instead applicant discusses the merit of Davison, which has been addressed above.

Claims 8, 19-20, 28-31, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davison (4879303) in view of Toth et al (WO 98/26765).

As set forth above, Davison et al teach a pharmaceutical composition containing amlodipine maleate. Davison teaches adjusting the pH of the composition to that of blood or close to blood pH for biocompatibility. Davison teaches the use of excipients for compression aids such microcrystalline cellulose.

Davison does not teach the use of an acid pH-adjusting agent.

Toth et al teach a stabilized pharmaceutical compositions containing enalapril maleate and the process for preparation. Toth teaches enalapril is useful in the treatment of hypertension. However, it is known in the art that these compounds are poorly stable either in the form of free acids or salts when in a pharmaceutical dosage form since they decompose by hydrolysis easily. Toth et al teach that this phenomena is especially true for enalapril and its maleate salt. Further, the salt extensively decomposes in the presence of conventional excipients such as microcrystalline cellulose or calcium phosphate. Thus, Toth teaches the use of maleic acid as a stabilizer to provide for a highly stable product that has a longer expiration time. See page 1 and 3. The reference teaches preparing the tablets or capsules by wet granulation. See page 4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Davison et al and Toth et al and utilize the instant acidic agent in Davison's teachings. One would be motivated to do so since Toth et al teach the use of maleic acid as a stabilizer for the maleate salt of enalapril.

One would expect similar results since Toth et al discuss the known instability of hypertensive compounds due to internal hydrolysis, as discussed by Davison concerning amlodipine, and the instability caused by conventional excipients such as microcrystalline cellulose and calcium phosphate, also taught by Davison; therefore a skilled artisan would be motivated to look at the guidance of Toth and proceed in a similar manner to avoid the process of hydrolysis known to take place in hypertensive compounds, especially concerning the maleate salt.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-242-0614. The examiner can normally be reached on M-F (8:00-5:00) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SSG

February 26, 2004

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